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The impact of sodium-glucose co-transporter-2 inhibitors on serum sodium and potassium in patients with Heart Failure: a systematic review and meta-analysis

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Abstract

Background Managing electrolyte abnormalities, particularly sodium and potassium, in patients with heart failure (HF) remains a concern. A novel anti-diabetic drug, sodium-glucose co-transporter-2 (SGLT2) inhibitors, has become suitable for HF patients, improving cardiovascular outcomes. Therefore, we aimed to conduct a meta-analysis to evaluate the effect of SGLT2 inhibitors on serum sodium and potassium.

Methods We systematically searched five databases, identifying randomized clinical trials (RCTs) reporting changes in serum sodium and potassium levels with SGLT2 inhibitors compared to comparator groups. Outcomes were presented as weighted mean differences (WMD) and standardized MD (SMD) with 95% confidence intervals (CI). Subgroup and sensitivity analyses were also conducted.

Results 13 studies were included, with 13 studies with 10,617 participants reporting on serum sodium and nine studies with 9877 participants on serum potassium. In acute HF, SGLT2 inhibitors did not significantly affect serum sodium (WMD: 1.21 mmol/L; 95% CI: − 0.79, 3.21) or potassium levels (WMD: 0.11 mEq/L; 95% CI: − 0.20, 0.42). Subgroup analyses suggested possible variations by follow-up duration (< 7 days vs. ≥ 30 days) and drug type, but findings remained non-significant. Sensitivity analysis using the leave-one-out method and risk of bias assessment results showed no considerable changes in the statistical significance of the pooled results. Similarly, in chronic HF, no significant differences were observed for serum sodium (WMD: 0.23 mmol/L; 95% CI: − 0.45, 0.91) or potassium (WMD: 0.07 mEq/L; 95% CI: − 0.29, 0.44). Sensitivity and subgroup analyses based on duration, drug type, diabetes status, renal function, or systolic blood pressure did not reveal clinically meaningful differences across all analyses. For all analyses, Egger's test was non-significant, indicating no strong evidence of small-study effects. Moreover, the trim-and-fill method combined with the funnel plot did not identify any missing studies, and the recalculated effect size remained unchanged.

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Conclusions SGLT2 inhibitors did not significantly alter serum sodium or potassium levels in acute or chronic HF, suggesting that these drugs can be safe regarding electrolyte disturbances. Additional RCTs are warranted to enhance the robustness of evidence regarding the mechanisms and effects of SGLT2 inhibitors on serum electrolyte levels, considering variations across different types of SGLT2 inhibitors.

Keywords Sodium-Glucose Transporter 2 Inhibitors, Serum Sodium, Serum Potassium, Heart Failure, Meta-Analysis

Introduction

Electrolyte imbalances, particularly alterations in serum sodium and potassium levels, are common in patients with heart failure (HF) and can have significant prognostic implications [1, 2]. Potassium abnormalities in HF can occur due to neurohormonal activation, use of drugs such as diuretics, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), old age, and concomitant underlying diseases, including diabetes mellitus (DM) and chronic kidney disease [3, 4]. Both hyperkalemia and hypokalemia are prognostic factors in patients with HF, predicting adverse outcomes such as arrhythmias and sudden cardiac death [5]. Moreover, sodium abnormalities, mainly hyponatremia (serum sodium < 135 mmol/L), are a common complication in hospitalized HF patients due to renin–angiotensin–aldosterone system activation and sympathetic overactivity, which causes impaired water excretion, and diuretic use in these patients causes sodium loss, exacerbating sodium imbalances [6–8]. Hyponatremia is less common in ambulatory rather than hospitalized HF patients (8.4% Vs. 20–25%); however, regardless of the acute or chronic condition of HF, hyponatremia can predict adverse clinical outcomes, including cardiovascular and all-cause mortality [1].

In recent years, sodium-glucose co-transporter-2 (SGLT2) inhibitors, novel antidiabetic agents, have been proven to improve outcomes in patients with HF, reducing HF hospitalization and mortality [9–11]. Renal glucose reabsorption from the glomerular filtrate depends on a tightly coordinated interplay between sodium (Na^+) and glucose transport in the renal tubules [12]. The key to this process is the sodium-glucose cotransporters, SGLT2 and SGLT1, which work in conjunction with the basolateral glucose transporters GLUT2 and GLUT [12]. SGLT2 inhibitors act on the kidney's proximal tubule, inhibiting glucose, and sodium reabsorption, causing a natriuretic and osmotic diuresis effect, which may alter serum electrolyte levels [1].

Therefore, several randomized clinical trials (RCTs) have investigated whether SGLT2 inhibitors alter serum sodium and potassium levels, resulting in controversial results. Although some trials reported increased serum sodium with SGLT2 inhibitors compared to placebo, other trials did not find a significant change in serum sodium in patients with chronic HF [1, 13–15]. In addition, trial results were inconsistent regarding serum potassium levels in chronic HF, with some results favoring a decrease and others mentioning no change in serum potassium levels [15–18]. Moreover, in acute HF settings, there have been several studies regarding the effect of SGLT2 inhibitors on decreasing serum sodium and potassium levels from admission to discharge, with some significant and insignificant results [19–22]. SGLT-2 inhibitors represent a significant advancement in managing acute and chronic HF; however, their use necessitates careful consideration of serum sodium and potassium dynamics to optimize treatment outcomes and minimize adverse events. Therefore, we conducted a meta-analysis of available RCTs to evaluate the impact of SGLT2 inhibitors on serum sodium and potassium levels in patients with HF.

Methods

Protocol and registration

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Table S1) [23] and registered in the International Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD42024513766.

Search strategy

We comprehensively searched five electronic databases, including Medline, Embase, Scopus, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov, covering the period from database inception to March 10, 2025. A manual search was also performed using Google and Google Scholar search engines to retrieve additional articles, and references were manually searched. The search queries for this systematic search are presented in Table S1. We included all parallel-group RCTs that reported serum sodium and potassium levels before and after SGLT2 inhibitor administration, compared to the control group. We excluded reviews, prospective or retrospective studies, case reports, commentaries, editorials, conference papers, abstracts, erratums, and animal

or cellular model studies. Moreover, we limited our selection to studies available in the English language.

Eligibility criteria

Four reviewers (M.Mo., M.Ma., A.E., and S.H.) independently screened the literature according to predetermined criteria for eligible articles: 1) RCTs that investigated and compared serum sodium and potassium levels before and after randomization to either SGLT2 inhibitors or control drugs with mean ± standard deviation (SD) in chronic or acute HF. 2) Treatment interventions included only SGLT-2 inhibitors. (3) Patients must be older than 18 years (adults). 4) The included studies must mention the duration of follow-up. The exclusion criteria were patients < 18 years and pregnant women.

Study selection and data extraction

Four reviewers (M.R.R., G.G.D., S.M., and A.P.A.) assessed the titles and abstracts of studies investigating the influence of SGLT2 inhibitors compared with the control group on serum sodium and potassium levels to identify duplicates and select relevant articles for further review. The full texts of potentially relevant studies were then independently examined to finalize the selection process. Records were screened using EndNote software version 21. However, certain studies presented continuous data in median and interquartile ranges, which is inconsistent with other articles excluded from the analysis. In cases where the required data were absent from the study, additional information was requested by emailing the corresponding author.

We extracted the following data from the included RCTs: Study characteristics (first author, year of publication, study design, and study site country), number of patients in SGLT2 inhibitor and control groups, type of SGLT2 inhibitor and dosage, participant characteristics at baseline (percentage of male and mean ± SD age), mean ± SD baseline left ventricular ejection fraction (LVEF), mean ± SD baseline estimated glomerular filtration rate (eGFR), mean ± SD baseline body mass index (BMI), and baseline used medication in chronic HF or medication used during hospitalization in acute HF (ACE inhibitor/ARB, mineralocorticoid receptor antagonist (MRA), beta-blockers, angiotensin receptor/neprilysin inhibitor (ARNI), thiazide diuretic, and loop diuretic), number of patients with DM, number of patients with hypertension, mean ± SD systolic blood pressure (SBP), and duration of follow-up. The primary outcome data were extracted as the mean ± SD serum sodium and potassium levels before and after SGLT2 inhibitor or control drug administration. Any discrepancies concerning the screening process or data extraction were resolved through discussion and consultation with two other reviewers (R.A.B. and B.D.). Data extraction and management were conducted using Microsoft Excel and Microsoft Word, respectively.

Quality assessment

We used the Cochrane Risk of Bias 2 (RoB 2) tool to evaluate RCTs [24], reporting the results as "high-risk," "low-risk," or "some concerns" risk of bias based on five domains presented in **Figure S2**. Two investigators (R.A.B. and B.D.) independently conducted the quality assessments. Any discrepancies were resolved through discussion with a third reviewer (D.SH.).

Statistical analysis

The results were quantitatively and qualitatively described. The association between SGLT2 inhibitors and serum sodium and potassium levels was expressed as a between-group weighted mean difference (WMD) with a 95% confidence interval (CI) and standardized mean difference (SMD), including Cohen's d and Hedges' g, with a 95% CI. The between-group (SGLT2i group vs. control group) SMD (95% CI) and SMD (95% CI) were calculated using either the raw data as the mean ± SD of serum sodium and serum potassium before and after SGLT2i administration or directly from the study data. The random-effects model (restricted maximum likelihood (REML)) was used to account for potential methodological heterogeneity among studies with Hartung–Knapp correction. Heterogeneity was assessed using the I^2 statistic, with thresholds interpreted as low (I^2 < 25%), moderate (I^2 25–50%), high (I^2 50–75%), and very high (I^2 > 75%).

In addition to primary analysis, subgroup analyses were conducted to determine the effects of SGLT2 inhibitors on serum sodium and potassium levels. These subgroup analyses were pre-specified based on clinically relevant factors, including duration of follow-up (≤ 7 days vs. ≥ 30 days for acute HF and ≤ 12 weeks vs. > 12 weeks for chronic HF), Type of SGLT2 inhibitor (Canagliflozin, Dapagliflozin, Empagliflozin), baseline SBP (< 130 mmHg vs. ≥ 130 mmHg), baseline estimated eGFR (< 60 vs. ≥ 60 and < 65 vs. ≥ 65 mL/min/1.73 m^2), and presence of DM (all patients with DM vs. mixed patients).

Sensitivity analyses were performed by systematically removing each study individually from the meta-analysis, using the leave-one-out method to evaluate the robustness of the findings. Additionally, low-quality studies (as per the RoB 2) were excluded from separate analyses to assess their influence on overall results. The small-study effect (publication bias) was evaluated using Egger's regression asymmetry test ($p < 0.10$, indicating potential bias), contour-enhanced funnel plots for visual inspection of asymmetry, and the trim-and-fill method to estimate

the number of missing studies and adjust the effect estimates accordingly. All statistical analyses were performed using Stata 17.0 (StataCorp, Texas, USA). Statistical significance was set at a two-tailed p-value of < 0.05.

Compliance with ethics guidelines

Ethics committee approval was not required for this systematic review, as it entailed synthesis and examination of pre-existing data derived from previously published investigations. Consequently, the ethics committee's approval was considered unwarranted.

Results

Search result and study selection

Initially, 7650 studies were identified across related databases, and after duplicate removal, 3260 studies remained. According to title and abstract screening, 308 studies were eligible for full-text assessment. Finally, 13 studies were included in this meta-analysis [14–16, 18–20, 25–31]: 13 reported on serum sodium changes [14–16, 18–20, 25–31] and 10 reported on serum potassium changes [15, 16, 18, 19, 25, 26, 29–31] after SGLT2 inhibitor treatment compared with the comparator group (Fig. 1).

Characteristics and quality assessment of included studies (Sodium and Potassium)

The baseline characteristics of the included studies are shown in Tables 1 and S3. This meta-analysis included 10,617 participants, 5295 of whom were in the SGLT2 inhibitor group and 5322 in the comparator group. The studies were published from 2017 to 2025, with follow-up periods ranging from 5 to 90 days in acute HF and 4 to 52 weeks in chronic HF. Seven studies used Dapagliflozin 10 mg, five used Empagliflozin 10 mg, and one used Canagliflozin 100 mg. Across the included cohorts, the mean (median) age ranged from approximately 55.8 to 79 years, with the proportion of male participants varying from 43 to 100%. The proportion of participants with DM varied widely across the included cohorts, ranging from 10.0% to 100%, with a median of approximately 42.4%. Among studies that reported hypertension status, the proportion of participants with hypertension ranged from 43.4% to 86.9% (mean ≈ 68%). Overall, nine RCT studies had a low risk of bias, one had some concerns about bias, and three were in the high risk of bias group (Figure S1).

SGLT2 inhibitor and serum sodium in acute heart failure

Six studies [19, 20, 25, 27, 30, 31] reported changes in serum sodium levels in acute HF, with 581 (61.1% male) in the SGLT2 inhibitor group and 588 (61.7% male) in the control group. A random-effects REML model with

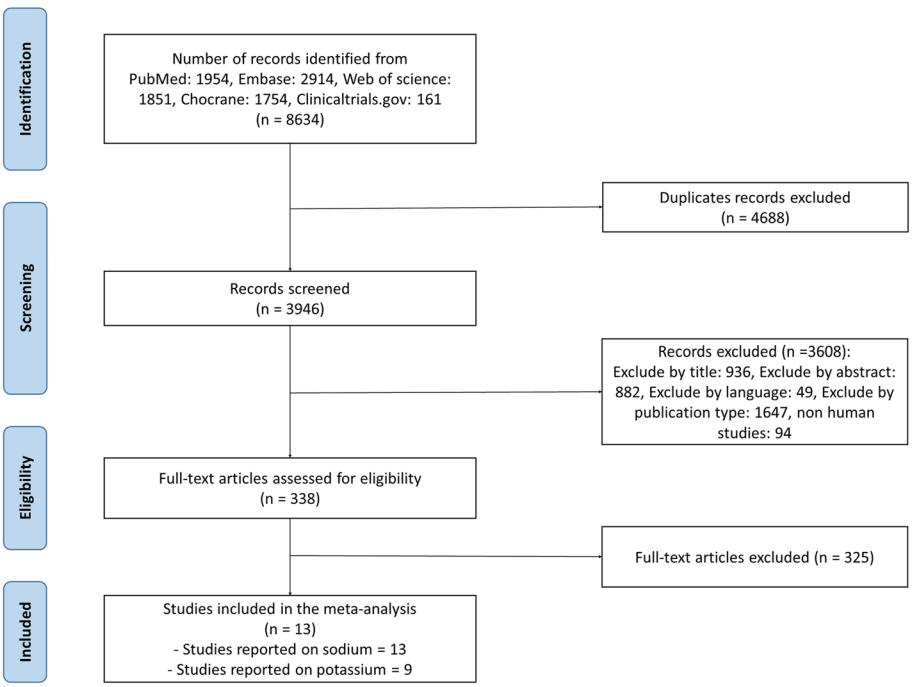

Fig. 1 PRISMA flow diagram of the literature search and selection of studies

Table 1 Baseline characteristics of the included randomized clinical trial studies

First author, year	Trial name	Country	Patients	Follow-up	Drug (Dosage)	No	Age (Male %)	LVEF	eGFR	BMI	DM %	HTN	SBP	Outcome	Quality assessment
Kawanami et al. [27], 2025	ROAD-ADHF (UMIN000044342)	Japan	ADHF	7 days	Dapagliflozin (10 mg)	56	74 [63–85] (62.5%)	35 [29–39]	NA	24.0 [19.9–27.5]	26.8	60.7	140 [123, 168]	Na	Low risk
					Conventional therapy	58	78 [70–85] (67.2%)	30 [25–36]	NA	23.6 [21.7-26.1]	15.5	62.1	137 [124–165]		
Charaya et al. [20], 2023	NCT04778787	Russia	AHF	5 days [4, 6]	Dapagliflozin (10 mg)	140	72 ± 12 (55.7%)	44 ± 14	55.6 ± 20	NA	31.4	85.7	130 ± 16	Na	High risk
					Placebo	145	75 ± 13 (50.3)	47 ± 13	52.0 ± 19	NA	38.6	86.7	128 ± 17		
Yeoh et al. [31], 2023	NCT04860011	Multicentric	worsening HF	5 days	Dapagliflozin (10 mg)	30	79 [73–86] (43%)	45 [6, 35–54]	40.7 [34.1–50.7]	32 [27–36]	63.3	NA	115 [104–128]	Na K	Low risk
					Metolazone (5 mg or 10 mg)	31	79 [68–84] (48%)	45 [6, 35–54]	40.7 [29.2–59.1]	33 [28–38]	29.0	NA	118 [109–127]		
Voors et al. [30], 2022	EMPULSE (NCT04157751)	Multicentric	AHF	90 days	Empagliflozin (10 mg)	265	71 [62–78] (60%)	31.0 [23.0–45.0]	50.0 [36.0–65.0]	28.3 [24.5–32.5]	46.8	77.4	120 [109.0–135.0]	Na K	Low risk
					Placebo	265	71 [62–78] (67.5%)	32.0 [22.5–49.0]	54.0 [39.0–70.0]	28.3 [24.5–32.5]	43.8	83.4	122 [110.0–138.0]		
Damman et al. [25], 2021	EMPA-RESPONSE-AHF (NCT03200860)	Netherlands	AHF	30 days	Empagliflozin (10 mg)	40	79 [73–83] (60.0%)	36 ± 17	55 ± 18	NA	37.5	67.5	127 ± 22	Na K	High risk
					Placebo	39	73 [61–83] (74.4%)	37 ± 14	55 ± 18	NA	28.2	56.4	121 ± 25		
Ibrahim et al. [19], 2020	NCT04385589	Egypt	AHF + DM + eGFR > 45	4.78 ± 1.29 days	Dapagliflozin (10 mg)	50	60.64 ± 9.9 (52%)	32.54 ± 2.99	NA	27.78 ± 2.3	100	56.0	110.74 ± 12.51	Na K	Some concerns
					Placebo	50	62.02 ± 8.8 (56%)	32.23 ± 2.49	NA	28.23 ± 3.3	100	62	113.08 ± 14.97		
Marton et al. [29], 2024	DAPA-Shuttle1 (NCT04080518)	Multicentric	Chronic HF	4 weeks	Dapagliflozin (10 mg)	15	55.8 ± 15.7 (80%)	33.4 ± 8.0	NA	29.1 ± 5.91	53.3	53.3	128 ± 19.9	Na K	Low risk
					Placebo	14	62.9 ± 10.5 (100%)	27.4 ± 8.5		26.4 ± 5.22	42.9	53.7	119 ± 14.3		
Packer et al. [18], 2023	EMPEROR-Reduced + EMPEROR-Preserved (NCT03057977 + NCT03057951)	Multicentric	HFrEF/ HFpEF	4 weeks	Empagliflozin (10 mg)	1961	70.3 ± 9.6 (60.7%)	NA	57.7 ± 20.2	NA	47.3	86.9	130.9 ± 18.3	Na K	Low risk
					Placebo	2020	70.3 ± 9.7 (60.9%)	NA	57.5 ± 20.0	NA	47.5	86.2	129.7 ± 17.4		
Docherty et al. [26], 2021 Shen et al. [17], 2021	DAPA-HF (NCT03036124)	United States	HFrEF + eGFR > 30	8 months	Dapagliflozin (10 mg)	2346	66.2 ± 11.0 (76.2%)	31.2 ± 6.7	66.0 ± 19.6	28.2 ± 6.0	41.8	NA	122.0 ± 16.3	Na K	Low risk
					Placebo	2345	66.5 ± 10.8 (77.0%)	30.9 ± 6.9	65.5 ± 19.3	28.1 ± 5.9	41.8	NA	121.6 ± 16.3		
Kolwelter et al. [28], 2021	NCT03128528	Germany	HFrEF/ HFmEF	3 months	Empagliflozin (10 mg)	48	67.7 ± 8.8 (81.3%)	43 [37–45]	74.1 ± 16.3	28.8 ± 3.9	25.0	72.9	122.8 ± 19.7	Na	Low risk
					Placebo	26	64.0 ± 8.8 (88.5%)	38 [28–43]	72.6 ± 19.9	29.4 ± 3.5	19.2	84.6	121.0 ± 17.1		

Table 1 (continued)

First author, year	Trial name	Country	Patients	Follow-up	Drug (Dosage)	No	Age (Male %)	LVEF	eGFR	BMI	DM %	HTN	SBP	Outcome	Quality assessment
Jensen et al. [15], 2021	Empire HF Renal (NCT03198585)	Denmark	HFrEF + GFR > 30	12 weeks	Empagliflozin (10 mg)	60	68 ± 10 (78.3%)	31 ± 7	70 ± 18	29.0 ± 4.4	15.0	NA	121 ± 17	Na K	Low risk
					Placebo	60	67 ± 10 (86.7%)	31 ± 7.5	73 ± 18	30 ± 5	10.0	NA	123 ± 16		
Tanaka et al. [16], 2020	CANDLE (number 000017669)	Japan	CHF + DM	24 weeks	Canagliflozin (100 mg)	113	68.3 ± 9.8 (77.9%)	57.4 ± 15	64.1 ± 15.3	NA	100	43.4	124.9 ± 14.2	Na K	High risk
					Glimepiride (initiation: 0.5 or 1 mg)	120	68.9 ± 10.4 (71.7%)	57.7 ± 14.2	63.3 ± 14.9	NA	100	44.2	124.5 ± 18.0		
Kosiborod et al. [14], 2017	NCT01031680, NCT01042977	Multicentric	HF + DM	52 weeks	Dapagliflozin (10 mg)	171	63.6 ± 7.5 (64.3%)	NA	68.8 ± 19.9	34.1 ± 5.8	100	NA	133.3 ± 14.7	Na	Low risk
					Placebo	149	64.9 ± 7.3 (61.1%)	NA	72.0 ± 19.2	34.3 ± 5.5	100	NA	134.2 ± 15.3		

Abbreviations: LVEF left ventricular ejection fraction, *eGFR* estimated glomerular filtration rate, *BMI* body mass index, *ACEi* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *MRA* mineralocorticoid receptor antagonist, *ARNI* angiotensin receptor/neprilysin inhibitor, *DM* diabetes mellitus, *HTN* hypertension, *SBP* systolic blood pressure, *AHF* acute Heart Failure, *NA* not available, *Na* sodium, *K* potassium, *HFrEF* heart failure with reduced ejection fraction, *HFpEF* heart failure with preserved ejection fraction, *CHF* congestive heart failure, *mg* milligrams

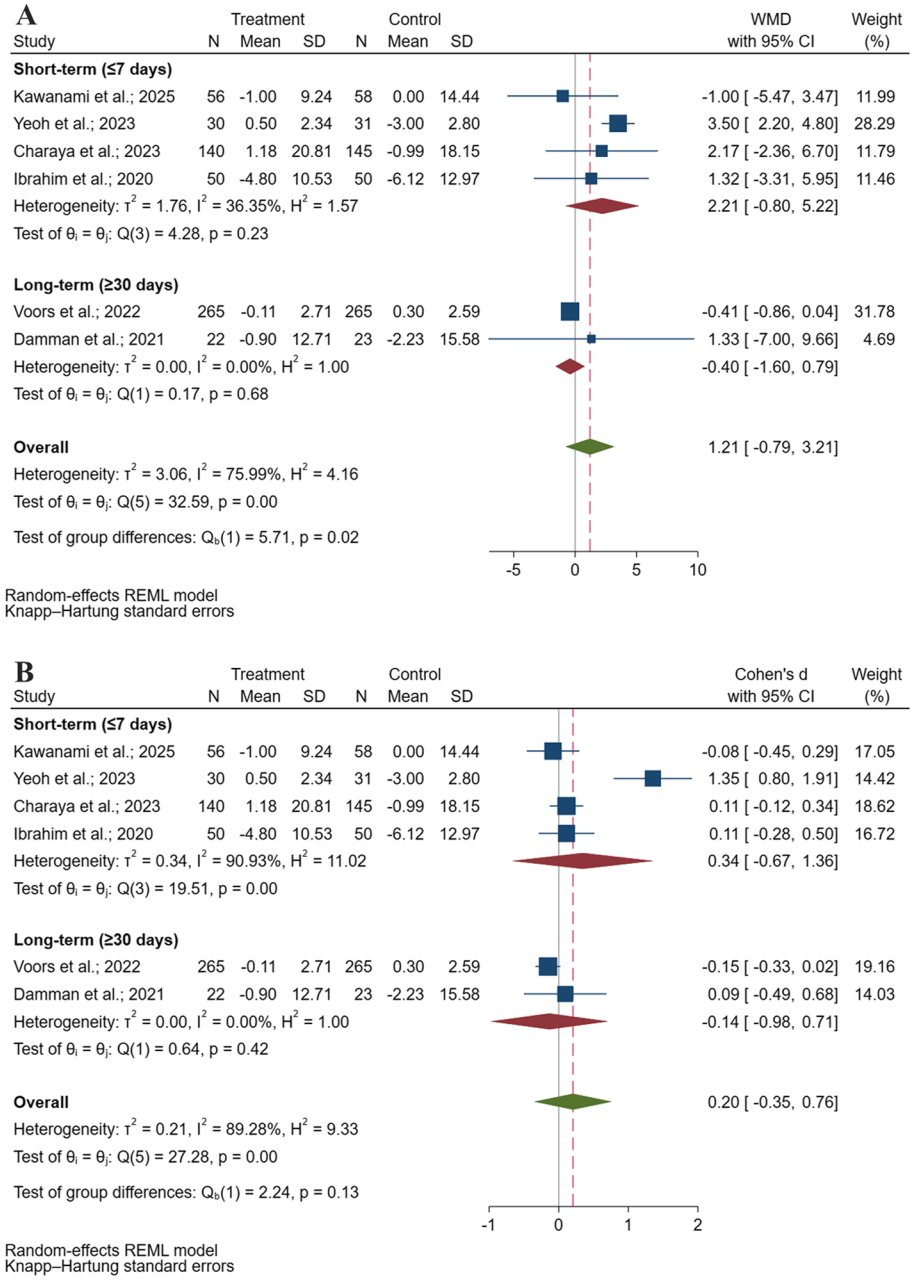

Fig. 2 Forest plot of randomized clinical trial studies assessing the effect of SGLT2 inhibitors on serum sodium levels in acute heart failure quantified by using the weighted mean difference (**A**) and standardized mean difference (**B**)

the Knapp-Hartung method yielded a pooled WMD of 1.21 mmol/L (95% CI: -0.79, 3.21), indicating no statistically significant effect on serum sodium, with a 95% prediction interval (PI) ranging from –4.11 to 6.53 (Fig. 2).

A subgroup analysis was conducted based on the duration of follow-up (≤7 days vs. ≥30 days) to more accurately examine the impact of SGLT2 inhibitors on serum sodium in acute HF over shorter and longer periods. In the short-term subgroup (≤7 days; four studies), the pooled WMD was 2.21 mmol/L (95% CI: -0.80, 5.22), with moderate heterogeneity ($I^2 = 36.35\%$). In addition, the long-term subgroup (≥30 days; 2 studies) demonstrated a WMD of -0.40 mmol/L (95% CI: -1.60, 0.79), accompanied by low heterogeneity ($I^2 = 0$) (Fig. 2A). The test of group differences indicated a statistically significant difference between the short-term and long-term follow-up periods ($p = 0.02$).

Table 2 Subgroup and sensitivity analysis of the effect of sodium-glucose co-transporter-2 inhibitors on serum sodium in chronic heart failure

Study group	Number of studies (number of patients)	Meta-analysis		Heterogeneity	
		WMD (95%CI)	P value	I^2 (%)	P between group
Follow-up duration					0.82
≤ 12 weeks [15, 18, 29]	3 (4130)	0.33 (-2.27, 2.94)	0.638	88.60	
> 12 weeks [14, 16, 26, 28]	4 (5318)	0.18 (-0.83, 1.19)	0.604	76.59	
Type of SGLT2 inhibitor					**0.02**
Canagliflozin [16]	1 (233)	-0.60 (-1.23, 0.03)	0.995		
Dapagliflozin [14, 26, 29]	3 (5040)	0.85 (-0.75, 2.45)	0.150	75.44	
Empagliflozin [15, 18, 28]	3 (4175)	0.00 (-0.01, 0.01)		0	
Mineralocorticoid receptor antagonist use					0.63
< 50% [14, 16, 18]	3 (4534)	0.09 (-1.81, 1.99)	0.859	86.95	
≥ 50% [15, 16, 26, 28, 29]	4 (4914)	0.37 (-0.95, 1.68)	0.441	79.37	
Type 2 Diabetes Mellitus					0.92
Mix [15, 18, 26, 28, 29]	5 (8895)	0.26 (-0.58, 1.11)	0.439	94.54	
All diabetes patients [14, 16]	2 (553)	0.18 (-9.98, 10.34)	0.862	88.82	
Systolic blood pressure					0.68
< 130 mmHg [15, 16, 26, 28]	5 (5147)	0.16 (-0.88, 1.20)	0.690	84.06	
> 130 mmHg [14, 18]	2 (4301)	0.41 (-5.84, 6.66)	0.558	81.85	
Estimated glomerular filtration rate					0.17
< 65 (mL/min/1.73 m^2) [16, 18]	2 (4214)	-0.21 (-3.86, 3.43)	0.594		
> 65 (mL/min/1.73 m^2) [14, 15, 26, 28]	4 (5205)	0.28 (-0.52, 1.08)	0.349		
Risk of bias assessment					**0.02**
Low-risk [14, 15, 18, 26, 28, 29]	6 (9215)	0.37 (-0.35, 1.08)	0.243	93.89	
High-risk [16]	1 (233)	-0.60 (-1.23, 0.03)			

Abbreviations: SGLT2 sodium-glucose co-transporter-2, *WMD* weighted mean difference, *P*, *p*-value

The pooled results based on Cohen's *d* method, also demonstrated non-significant results in both short-term (Cohen's *d*: 0.34; 95% CI: -0.67, 1.36; $I^2 = 90.93\%$) and long-term (Cohen's *d*: -0.14; 95% CI: -0.98, 0.71; $I^2 = 0$) follow ups (Fig. 2B). The test of group differences did not indicate a statistically significant difference between the short-term and long-term subgroups ($p = 0.13$) (Table 2).

Several other subgroup analyses were performed to examine the potential effect of drug type (Empagliflozin vs. Dapagliflozin), MRA use (≥ 50%), or baseline SBP (≥ 130) influenced the effect of SGLT2 inhibitors on serum sodium in acute HF. In each subgroup, the WMD was individually non-significant, and no between-group differences emerged. Only the subgroup analysis by drug type revealed a significant between-group difference ($p = 0.02$), suggesting that the impact of SGLT2 inhibitors may vary according to the specific agent used, even though each agent's individual WMD was non-significant. The WMD remained nonsignificant across all quality-based subgroups (high-quality, low-quality, or some concerns), and no between-group differences reached statistical significance.

Leave-one-out sensitivity analysis showed negligible changes in the magnitude and statistical significance of the pooled results (all $p > 0.05$). Egger's regression test for small-study effects yielded a non-significant result ($p = 0.103$), suggesting no strong evidence of small-study effect. The contour-enhanced funnel plot appeared symmetrical, suggesting no substantial small study effect (Fig. 6A). The trim-and-fill procedure did not impute any missing studies, and the recalculated effect size remained unchanged.

SGLT2 inhibitor and serum sodium in chronic heart failure

Seven studies [14–16, 18, 26, 28, 29] reported on serum sodium changes in chronic HF, with 4714 (69.5% male) in the SGLT2 inhibitor group and 4734 patients (69.8% male) in the control group. The pooled analysis using a random-effects REML model with Knapp-Hartung modification demonstrated a non-significant WMD of 0.23 mmol/L (95% CI: -0.45, 0.91, $p = 0.43$) with a 95%

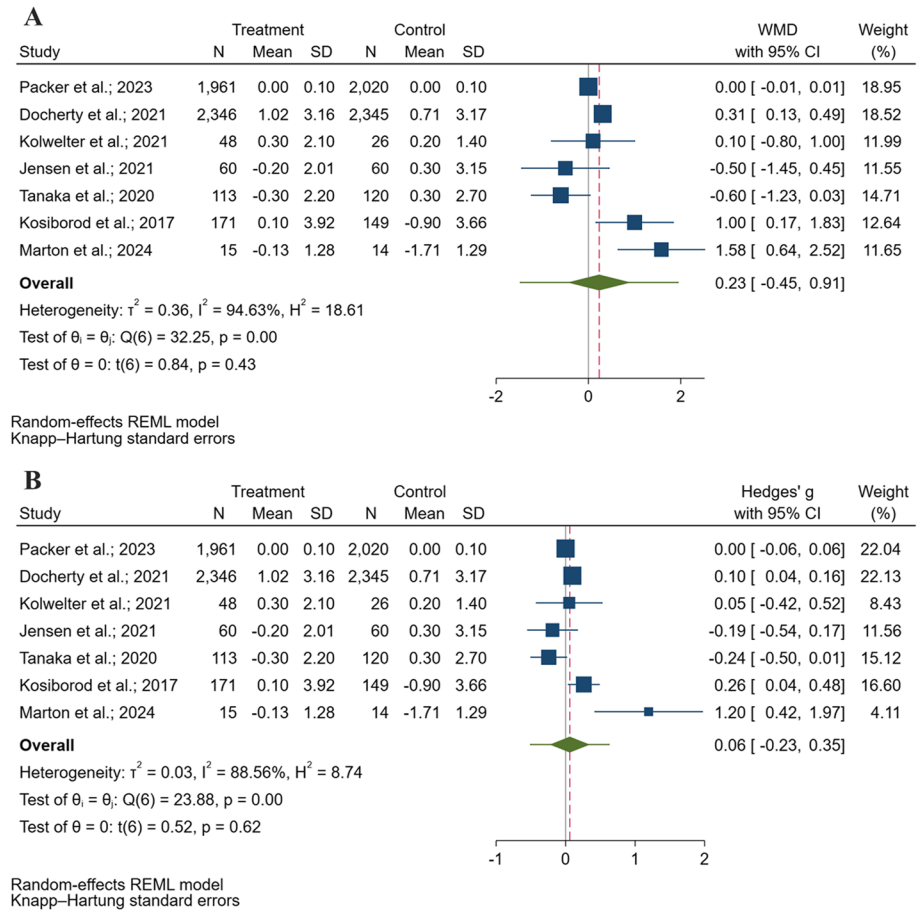

Fig. 3 Forest plot of randomized clinical trial studies assessing the effect of SGLT2 inhibitors on serum sodium levels in chronic heart failure quantified by using the weighted mean difference (**A**) and standardized mean difference (**B**)

PI ranging from -1.47 to 1.94 (Fig. 3A). The SMD using Hedge's *g* method also indicated a non-significant pooled effect size of 0.06 (95% CI: -0.23, 0.35, $p = 0.62$) (Fig. 3B). Both analyses showed very high heterogeneity (WMD: $I^2 = 94.63\%$, Hedge's *g*: $I^2 = 88.56\%$).

Subgroup analyses were conducted to evaluate whether follow-up duration (> 12 weeks), drug type (Empagliflozin, Dapagliflozin, or Canagliflozin), MRA use (≥ 50% of patients), diabetes status (all patients or mix), baseline SBP (> 130 mmHg), or baseline GFR (> 65 ml/min/1.73m^2) modified the effect of SGLT2 inhibitors on serum sodium levels in chronic HF. In each subgroup, the WMD remained non-significant, and no between-group differences reached statistical significance, except for drug type, which had a significant group difference ($p = 0.02$). These findings indicate that none of the examined factors significantly altered the effect of SGLT2 inhibitors on serum sodium in this patient population. Additionally, sensitivity analysis based on study quality assessment did not alter the overall findings, underscoring the robustness of the meta-analysis results.

Sensitivity analysis using the leave-one-out method showed no considerable change in the magnitude, direction, and statistical significance of the pooled results (all $p > 0.05$). Egger's regression test for small-study effects confirmed the absence of significant bias ($p = 0.159$). A contour-enhanced funnel plot was used in conjunction with the trim-and-fill method to evaluate potential small-study effects (Fig. 6B). The analysis identified no missing studies requiring adjustment, and the recalculated effect size remained non-significant.

SGLT2 inhibitor and serum potassium in acute heart failure

Four studies [19, 25, 30, 31] reported changes in serum potassium levels in acute HF, including 385 patients (62.9% male) in the SGLT2 inhibitor group and 385 patients (65.2% male) in the control group. A random-effects REML model (Knapp-Hartung modification) of four studies revealed a non-significant WMD of 0.11 mEq/L (95% CI: −0.20, 0.42) for serum potassium, with a 95% PI spanning −0.78 to 1.00. The heterogeneity was very high ($I^2 = 89.86\%$) (Fig. 4).

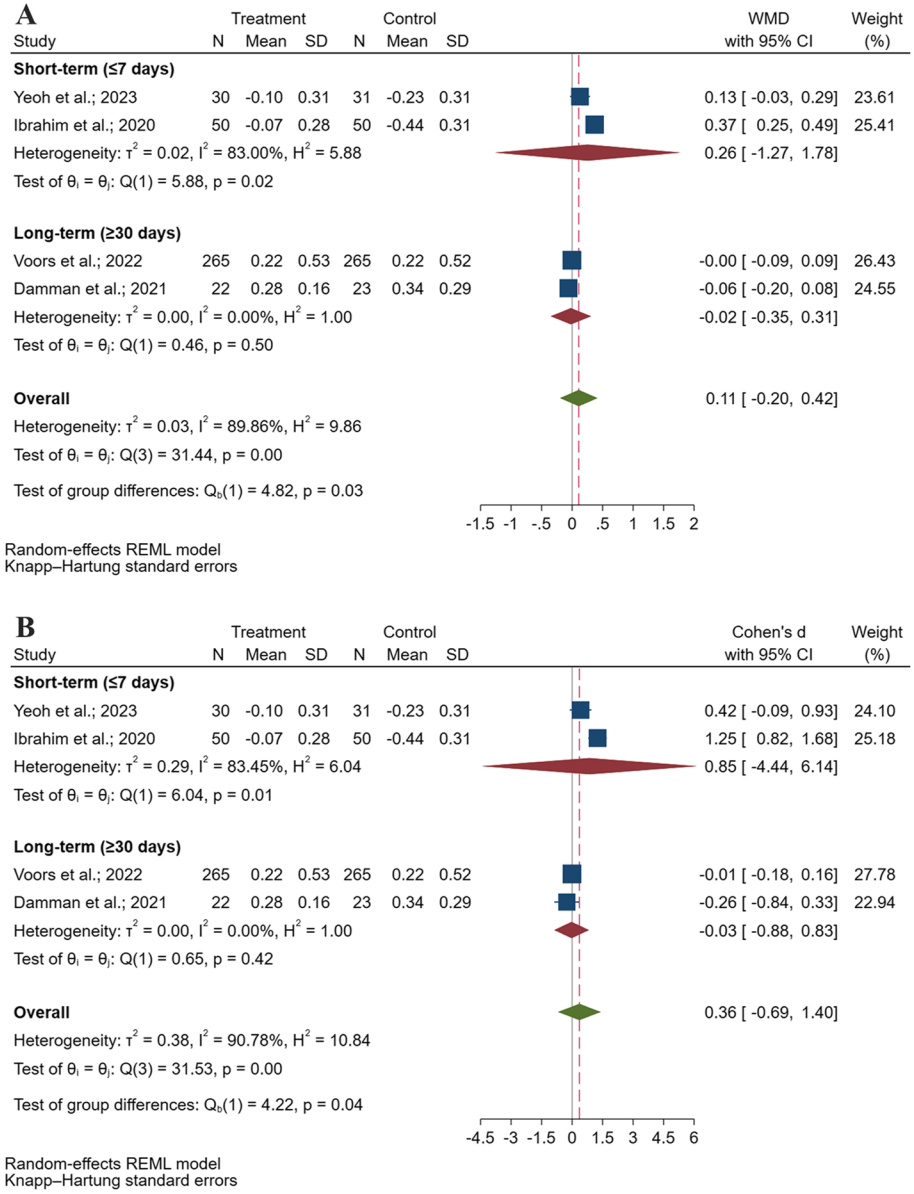

Fig. 4 Forest plot of randomized clinical trial studies assessing the effect of SGLT2 inhibitors on serum potassium levels in acute heart failure quantified by using the weighted mean difference (**A**) and standardized mean difference (**B**)

We also compared short-term (≤7 days) and long-term (≥30 days) follow-ups as subgroups. In the short-term subgroup (2 studies), the pooled WMD was 0.26 (95% CI: -1.27, 1.78; $I^2 = 83\%$), whereas in the long-term subgroup (2 studies), the WMD was -0.02 (95% CI: -0.35, 0.31; $I^2 = 0\%$;) (Fig. 4A). The difference between the groups was significant ($p = 0.03$). Using Cohen's *d*, the short-term subgroup showed a pooled effect of 0.85 (95% CI: −4.44, 6.14; $I^2 = 83.45\%$), while the long-term subgroup yielded -0.03 (95% CI: -0.88, 0.83; $I^2 = 0\%$) (Fig. 4B). The overall effect size was 0.36 (95% CI: −0.69, 1.40), accompanied by very high heterogeneity ($I^2 = 90.78\%$). The test of group differences was also significant ($p = 0.04$).

Subgroup analyses by drug type (Empagliflozin vs. Dapagliflozin) showed a significant between-group difference ($p = 0.03$), indicating that the impact on serum potassium may differ according to the specific agent. By contrast, MRA use (< 50% vs. ≥ 50%) did not reveal a significant difference ($p = 0.47$). Neither subgroup showed significant results. Sensitivity analysis by study quality (low vs. high risk of bias) also showed

a significant difference between groups ($p < 0.001$), with insignificant results within each group. However, the leave-one-out analysis demonstrated that omitting individual studies did not substantially alter the overall effect size or the significance level. Egger's test was non-significant ($p = 0.958$), indicating no strong evidence of small-study effects. A contour-enhanced funnel plot appeared symmetrical, and the trim-and-fill procedure did not impute any missing studies, suggesting a minimal small-study effect (Fig. 6C).

SGLT2 inhibitor and serum potassium in chronic heart failure

Five studies [15–18, 29] reported serum potassium changes in chronic HF, including 4522 patients (69.6% male) in the SGLT2 inhibitor group and 4585 patients (70.0% male) in the control group. Based on the REML random-effects model with Knapp-Hartung modification, the overall WMD for serum potassium was 0.07 (95% CI: -0.29, 0.44; $p = 0.61$) with very high heterogeneity ($I^2 = 99.62\%$), suggesting no significant change with SGLT2 inhibitors compared to the control (Fig. 5A). The 95% PI was reported as -0.951 to 1.096 for future studies on serum potassium levels. Moreover, the pooled Hedge's g was 0.23 (95% CI: −1.04, 1.50; $p = 0.64$), indicating a non-significant effect with a very high heterogeneity ($I^2 = 99.64\%$) (Fig. 5B).

Subgroup analyses were conducted based on the follow-up duration (> 12 weeks), drug type (Empagliflozin, Dapagliflozin, or Canagliflozin), MRA use (≥ 50% of patients), DM status (all patients or mix), baseline SBP (> 130 mmHg), and eGFR thresholds (GFR > 65 ml/min/1.73m^2). Overall, most subgroup effects were non-significant. However, the < 50% MRA subgroup yielded a significant result (WMD = 0.01; 95% CI: 0.01, 0.01; $p = 0.004$) with an insignificant between-group difference ($p = 0.65$). Similarly, the mean eGFR < 65 ml/min/1.73m^2 subgroup showed a significant effect (WMD = 0.01; 95% CI: 0.01, 0.01; $p = 0.004$), although the difference between the eGFR > 65 and eGFR < 65 ml/min/1.73m^2 subgroups was not significant ($p = 0.74$).

Additionally, sensitivity analysis based on quality assessment did not yield statistically significant differences. Likewise, the leave-one-out analysis revealed no major changes in the pooled effect size or p-values when each study was omitted. Egger's test for small-study effects was non-significant ($p = 0.46$), indicating no strong evidence of small-study effect. The contour-enhanced

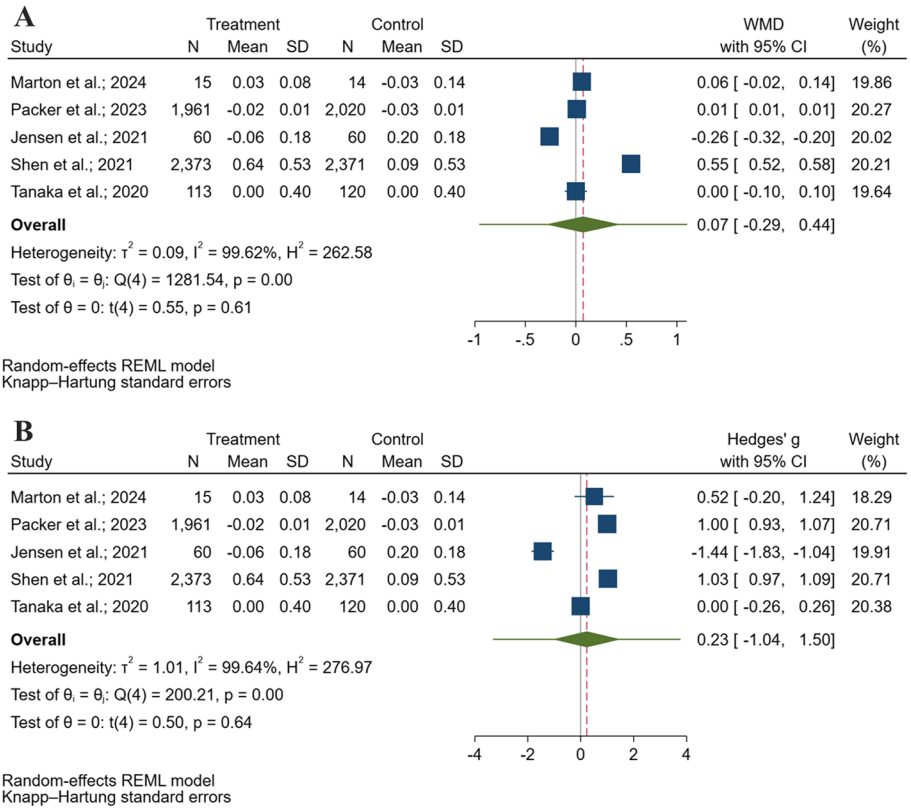

Fig. 5 Forest plot of randomized clinical trial studies assessing the effect of SGLT2 inhibitors on serum potassium levels in chronic heart failure quantified by using the weighted mean difference (**A**) and standardized mean difference (**B**)

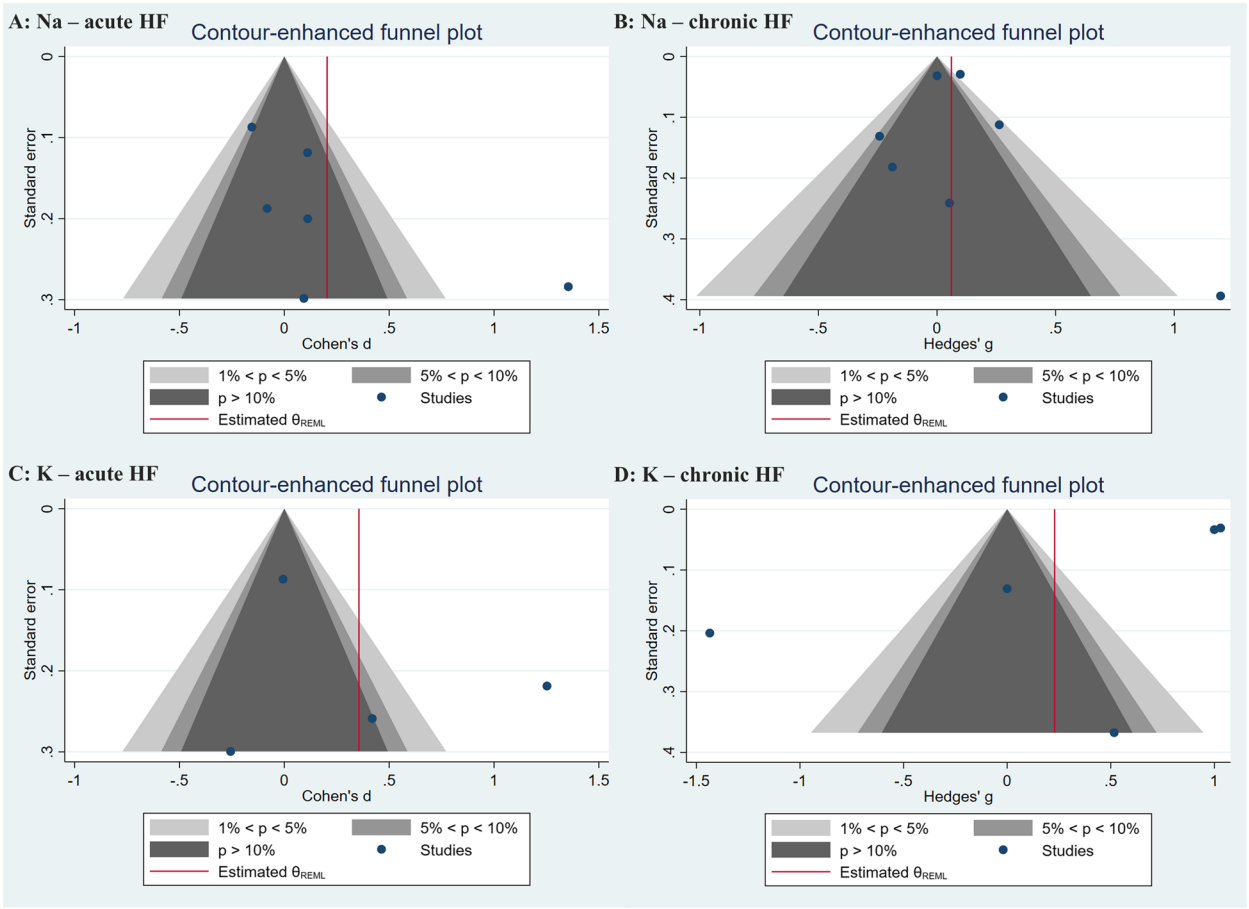

Fig. 6 Contour-enhanced funnel plots for SGLT2 inhibitor effects on serum sodium in acute (**A**) and chronic (**B**) heart failure, and serum potassium in acute (**C**) and chronic (**D**) heart failure. Shading indicates *p*-value contours, and the red vertical line denotes the pooled effect estimate

funnel plot appeared largely symmetrical, suggesting no major small study effect (Fig. 6D). The trim-and-fill method combined with the funnel plot did not identify any missing studies, and the recalculated effect size remained unchanged.

Discussion

In this meta-analysis, SGLT2 inhibitors did not induce a significant overall change in serum sodium or serum potassium compared with the control and exerted a neutral effect on both electrolytes, although substantial heterogeneity was observed in both the acute and chronic HF populations. The WMD was utilized as the primary measure to quantify clinically interpretable electrolyte changes. Additionally, standardized effect sizes such as Cohen's d and Hedge's g were calculated to account for variations in measurement scales and consistency across these effect size measures further strengthened our findings. Subgroup analyses (e.g., drug type, follow-up duration, baseline SBP, or MRA use) generally revealed non-significant differences; however, some subgroup analyses (e.g., short- vs. long-term follow-up, drug type) revealed minor differences, and none showed a consistent or clinically meaningful impact. A small-study effect was not evident, and the sensitivity analyses confirmed the stability of the findings. Overall, these results suggest that SGLT2 inhibitors have a neutral to modest impact on serum sodium and potassium levels in both acute and chronic HF, with certain clinical subgroups warranting further investigation. These results suggest that SGLT2 inhibitors can be safely used in diverse HF populations without major concerns of significant electrolyte imbalances.

Hyponatremia is a common condition in patients with HF due to various mechanisms, including neurohormonal activation and increased sodium and water reabsorption in the kidneys, which increases plasma volume, elevated sympathetic activity, constriction of splanchnic arteries and veins, blood shift from splanchnic vessels to the overall circulation, and potential dilutional

hyponatremia [32–35]. In patients with HF, SGLT2 inhibitors regulate serum sodium balance through several mechanisms. SGLT2 inhibitors reduce sodium reabsorption in the proximal convoluted tubule and prompt sodium reuptake in the distal region to prevent sodium waste [36]. These medications increase the urinary excretion of glucose and sodium, and promote glycosuria, natriuresis, and osmotic diuresis, which enhances sodium excretion [37, 38]. It has been suggested that SGLT2 inhibitors may function similarly to loop diuretics, excreting free water by diuresis, without hindering dilution of the distal nephrons, thus improving hyponatremia [39, 40]. In addition, inhibition of sodium reuptake can lead to better delivery of sodium to the loop of Henle, which improves the function of loop diuretics [41]. However, SGLT2 inhibitors minimally activate the neurohormonal system and cause insignificant changes in the patient's electrolyte profile, which differs from traditional diuretics [19, 42].

SGLT2 inhibitors uniquely mobilize sodium and fluid from the interstitium to the vascular space, potentially improving the renal blood flow [43, 44]. Decreased effective circulatory volume triggers baroreceptors and neurohumoral activation, including non-osmotic vasopressin secretion, a key factor in dilutional hyponatremia in acute HF [35]. SGLT2 inhibitors interstitial action and intravascular volume replenishment may help correct hyponatremia, which is why these drugs are more effective in hyponatremic patients than in normonatremic patients [20, 45]. SGLT2 inhibitors also decrease renin, increasing sodium delivery to the macula densa, affecting volume homeostasis, and potentially hyponatremia in acute HF [46]. In addition, treating hyponatremia involves balancing magnesium and potassium levels, and SGLT2 inhibitors have improved hypomagnesemia in DM without affecting serum potassium [35, 47, 48]. Finally, SGLT2 inhibitors can potentially reduce the need for other classes of diuretics, such as thiazide diuretics, and make them beneficial in managing acute HF [20, 45].

Loop diuretics are a primary management strategy for patients with acute HF and concomitant fluid overload [49]. Nonetheless, a substantial proportion of these patients show suboptimal responses, with up to 50% being resistant to diuretics [50]. Distally acting diuretics, specifically thiazide or thiazide-like agents, are frequently used along with loop diuretics to reduce resistance during therapeutic interventions [6]. Diuretics may stimulate the renin–angiotensin–aldosterone system (RAAS) at higher dosages, exacerbating HF [51]. Additionally, excessive diuretic administration can induce plasma volume contraction, worsening renal function, and disturbances in electrolyte balance, including hypokalemia, hypomagnesemia, hypocalcemia, hyponatremia, and hyperuricemia [52, 53]. Previous studies have demonstrated that SGLT2 inhibitors can reduce the need for and dosage of other classes of diuretics in acute HF and enhance the response to diuretics [25, 54, 55].

Shirakabe et al. observed that administering SGLT2 inhibitors significantly reduced loop diuretic dosages in diabetic patients with acute compensated HF [56]. In addition, time-dependent variations in renal tubular injury markers were observed between the empagliflozin and control groups, and a decrease in loop diuretic dosage and subsequent erythropoietin production may have mitigated renal tubular injury [56]. These mechanisms could be linked to HF outcomes, including mortality and rehospitalization rates [56]. In addition, Ibrahim et al. observed that dapagliflozin demonstrated notable diuretic effects in decompensated HF management in diabetic patients [19]. Its administration enhances loop diuretic efficacy while reducing the required dosage, with minimal impact on serum potassium levels or renal performance [19]. In this meta-analysis, loop diuretic use was reported across studies, but varied widely in dosing, administration, and duration, precluding a detailed analysis of its impact on outcomes.

Previous literature generally indicated that SGLT2 inhibitors may have a negligible or modest reducing effect on the need for additional diuretics, which could further support their role in optimizing diuretic therapy [19, 56]. Moreover, Charaya et al. found that in patients with acute HF, dapagliflozin increased serum sodium concentrations and reduced the persistence of hyponatremia, effects that emerged within the first 48 h of treatment and persisted until discharge [20]. Notably, this benefit was more pronounced among individuals presenting with hyponatremia at baseline, highlighting the valuable role of SGLT2 inhibitors in managing electrolyte imbalances in acute HF [20]. These findings reinforce the broader utility of SGLT2 inhibitors beyond their hemodynamic and glucose-lowering effects, suggesting their potential advantages in addressing common complications such as hyponatremia. Although our findings in acute HF showed no significant overall change in serum sodium, we noted a significant difference between the short- and long-term follow-up periods. This suggests that SGLT2 inhibitors may exert different effects during the acute or hospitalized phase compared with prolonged treatment. However, neither subgroup was independently significant and the limited number of RCTs calls for further research to clarify these observations.

The standard management of acute AHF typically involves loop diuretics for volume control and vasodilators (ACE inhibitors or ARBs) to improve hemodynamics and reduce cardiac stress, although these can be limited by diuretic resistance and potential renal or hypotensive

complications [57, 58]. Adding an SGLT2 inhibitor like dapagliflozin offers notable benefits, including a reduction in in-hospital cardiovascular mortality and 30-day readmissions [57]. By enhancing diuresis and improving cardiac function, dapagliflozin aids in weight reduction, largely owing to better fluid management, without significantly increasing the incidence of hypotension, renal deterioration, and worsening HF [57]. As a result, dapagliflozin serves as a promising adjunct to conventional therapies, helping address the gap in effective acute HF management.

Similar to acute HF, no significant effect was observed from SGLT2 inhibitors on serum sodium in patients with chronic HF. This association was also insignificant in several sub-analyses. However, each subgroup included fewer than five studies, limiting the robustness of these findings and underscoring the need for larger, well-powered trials. In line with our results, a meta-analysis by Zhang et al. found that the effect of SGLT2i on serum sodium levels in patients with DM was not significant [48]. However, it has also been reported that new hyponatremia is significantly lower in patients randomized to dapagliflozin compared to placebo at 4, 8, and 12 months after follow-up, and these patients are more likely to show resolution of baseline hyponatremia over time [1]. These findings suggest that despite an overall neutral effect on serum sodium in many settings, SGLT2 inhibitors may still help stabilize sodium levels over time, reducing the likelihood of new or persistent hyponatremia in certain populations.

Our results demonstrated no clinically significant effect of SGLT2 inhibitors on the mean serum potassium changes in chronic and acute HF; however, a small number of RCTs were included in our study. Three mechanisms mainly cause changes in serum potassium by SGLT2 inhibitors: First, osmotic diuresis and natriuresis caused by SGLT2 inhibitors can lead to increased distal flow and sodium supply in the distal tubule and, therefore, increased aldosterone levels [59, 60]. Second, increased glucagon levels can increase potassium excretion [61]. Third, SGLT2 inhibitor-induced glucosuria can decrease glucose and insulin levels and redistribute potassium from cells into the extracellular volume [39, 62]. The first two mechanisms cause kaliuresis and reduce serum potassium levels; however, the third mechanism has the opposite effect, and the interaction between these mechanisms can lead to a slight change in serum potassium [60].

Our finding aligns with another meta-analysis of patients with DM, which showed that SGLT inhibitors did not lead to a significant change in serum potassium, and this result was similar for different types of SGLT2 inhibitors [48]. Nevertheless, a recent meta-analysis in 2022 showed that after 208 weeks of use of SGLT2 inhibitors in DM patients, mean serum potassium significantly reduced by -0.07 mmol/L (95% CI: -0.11, -0.03), which still shows the low effect of these drugs on the serum potassium level in the long-term use [63]. In addition, SGLT2 inhibitors significantly reduce the risk of severe hyperkalemia (serum potassium $\geq$ 6.0 mmol/L) in patients with and without HF by 17% and 18%, respectively [63].

Concomitant medications are an important confounding factor for serum potassium levels and the risk of hypokalemia and hyperkalemia. In studies by Shen et al. (patients on MRA therapy) and Neuen et al. (patients on RAAS therapy)—both high-risk for hyperkalemia—SGLT2 inhibitors reduced severe hyperkalemia by 50% and 22%, respectively, suggesting that SGLT2 inhibitors can play a role in potassium balance [17, 63]. It is also noteworthy that higher baseline potassium levels are commonly observed in patients already receiving MRA and RAASi therapy, possibly because of underlying conditions such as DM, HF, or impaired kidney function that often necessitate these medications [2]. These characteristics could put the patient at risk of hyperkalemia and lead to cessation or reduction of the MRA or RAASi dose, which worsens HF prognosis [64–66]. Therefore, SGLT2 inhibitors can reduce the incidence of hyperkalemia and can be used with MRA or RAAS to make it safer [2]. Ferreira et al. observed that patients receiving empagliflozin continued MRA more frequently in a follow-up study [67]. Consistent with these findings, our subgroup analysis in chronic HF revealed no significant difference in serum potassium when SGLT2 inhibitors were used alongside MRA or RAASi therapy, supporting their safe co-administration for maintaining potassium balance.

In addition to RAAS inhibitors and MRA therapy, loop diuretics represent another key medication commonly co-administered in patients with HF that may affect electrolyte levels, particularly sodium [49, 52]. The natriuretic effect of loop diuretics may interact with SGLT2 inhibitor's mechanism of action, potentially influencing the observed changes in serum potassium levels in acute HF [19]. In our meta-analysis, owing to the insufficient number of included RCTs, it was not possible to perform meta-regression and evaluate the effect of loop diuretics.

Finally, although several subgroup analyses for sodium revealed differences between some populations, these differences may not be clinically significant in clinical practice. For example, clinically significant serum sodium changes are typically defined as a 4–6 mmol/L shift within hours in acute cases and a 10–12 mmol/L change per day in chronic conditions [68, 69]. Also, clinically significant changes in serum potassium typically involve fluctuations of 0.5–1.0 mmol/L or more [70], which were not observed in our included studies. Therefore, the

small effects of SGLT2 inhibitors on sodium and potassium levels in our analysis lack clinical relevance, as they fall within a range unlikely to impact the routine clinical management of patients with HF. These findings emphasize the need for careful interpretation.

This study has some limitations. The studies in the meta-analysis varied in terms of patient characteristics and treatment protocols, which could have introduced heterogeneity into the analysis. Despite efforts to comprehensively search multiple databases and obtain incomplete data in studies, the number of eligible RCTs included in this meta-analysis was relatively small. This limited sample size may have affected the robustness and reliability of our findings. In addition, because each subgroup contained fewer than five studies, these results must be interpreted cautiously. Owing to the small number of included studies and the need for at least ten studies for meta-regression, it was not possible to conduct meta-regression on any of the variables. Drawing definitive conclusions on this topic remains challenging, and additional RCTs are needed to provide greater clarity.

Conclusion

In conclusion, our meta-analysis provides valuable insights into the impact of SGLT2 inhibitors on serum sodium and potassium levels in patients with HF. We found that SGLT2 inhibitors did not significantly change serum sodium levels in patients with acute and chronic HF. Similarly, regarding serum potassium levels, our analysis showed no clinically significant effect of SGLT2 inhibitors in either acute or chronic HF patients. Although these medications may lead to slight changes in serum potassium levels, the overall impact was not statistically significant. Future research, including large-scale RCT studies with longer follow-ups, should focus on elucidating the mechanisms underlying the differential effects of SGLT2 inhibitors on electrolyte balance in acute and chronic HF and further explore the clinical implications of these findings in real-world practice. Such insights will contribute to refining treatment strategies and improving the care of HF.

Abbreviations

HF	Heart failure
SGLT2	Sodium-Glucose Transporter 2
CI	Confidence interval
SBP	Systolic blood pressure
eGFR	Estimated glomerular filtration rate
ACE	Angiotensin-converting enzyme
ARB	Angiotensin receptor blocker
DM	Diabetes mellitus
RCT	Randomized clinical trial
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis
PROSPERO	International Prospective Register of Systematic Reviews
SD	Standard deviation
LVEF	Left ventricular ejection fraction
BMI	Body mass index
MRA	Mineralocorticoid receptor antagonist
ARNI	Angiotensin receptor/neprilysin inhibitor
WMD	Weighted mean difference
RAAS	Renin-angiotensin-aldosterone system
HTN	Hypertension; AHF = acute heart failure
NA	Not available
Na	Sodium
K	Potassium
HFrEF	Heart failure with reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
CHF	Congestive Heart Failure
Mg	Milligram
P	P-value

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12872-025-04704-w.

Additional file 1: Figure S1: Risk of Bias 2 tool results of included randomized controlled trials. Table S1: PRISMA checklist. Table S2: Search strategy

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Authors' contributions
Conceptualization: [D. Sh.] and [M.H.]; Methodology: [R.A.B.] and [B.D.]; Investigation and Literature Search: [M.Mo], [M.Ma], [A.E], and [S.H]; Data Curation: [R.A,B.], [B.D.], [M.R.R], [Gh.Gh.D.], [S.M.], and [A.P.A.]; Writing-Original Draft: [R.A,B.], [B.D.], [M.R.R], [Gh.Gh.D.], [S.M.], and [A.P.A.]; Writing—Review and Editing: [D.Sh.], [M.Mo], [M.Ma], [A.E], [S.H], and [M.H.]; Visualization: [R.A.B.], [E.A.S]; Supervision and Project administration: [R.A.B.], [M. H.], and [D.Sh.].

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Data availability
Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

Declarations

Ethics approval and consent to participate
This article is based on previous studies and does not contain any new studies with human participants or animals performed by any of the authors.

Consent to publication
Not applicable.

Competing interests
The authors declare no competing interests.

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